REMARKS

Claims 35, 46, 59, 60, 64-66, and 68-90 are pending with claims 46 and 69-84 currently under examination. Applicants amended claims 46, 70, 72, 74, 76, 78, and 80 to include a mitochondrial localization sequence. The specification (WO 02/061105) supports this amendment at, for example, page 7, lines 6-12 and 15-16, and in original claim 15. Thus, this amendment to claims 46, 70, 72, 74, 76, 78, and 80 does not introduce new matter.

Claims 46 and 69-84 remain rejected under 35 U.S.C. § 103(a) as allegedly obvious over Aqeilan et al., *FEBS Lett.* 457(2):271-76 (1999) ("Aqeilan") in view of Kim et al., *J. Immunol.* 159(4):1666-68 (1997) ("Kim"), U.S. Patent 6,713,280 ("Huang"), U.S. Patent 6,235,872 ("Bredesen"), Sela and Zisman, *FASEB J.* 11(6):449-56 (1997) ("Sela"), and U.S. Patent 6,342,221 ("Thorpe"). Office Action at 2. According to the Office, Huang teaches a method of using peptide conjugates for intracellular targeting of Bcl-2, where the peptides include the sequence set forth in SEQ ID NO: 239. *Id.* at 3. Bredesen allegedly teaches linking the peptide sequence set forth in SEQ ID NO: 269 to a number of proapoptotic peptides because the peptide sequence set forth in SEQ ID NO: 269 does not alter the function of the peptide it is attached to and is allegedly well known for facilitating cellular entry. *Id.* The Office reads Kim as teaching the ability of the HIV-1 tat protein to transport macromolecules into cells and identifying a motif that is present in SEQ ID NO: 269, RKKRRQRRR, as necessary for functional translocation. The Office relies on Sela for the alleged teaching that inclusion of D-amino acids may be an advantage in terms of specificity and efficacy because of longer persistence while Aqeilan allegedly teaches a chimeric protein comprising an apoptosis-inducing protein, the human Bax protein, for targeted therapy. *Id.* at 4.

The Office now adds Thorpe to this obviousness rejection because Huang, Bredesen, Kim, Sela, and Aqeilan do not teach a cleavable peptide linker. Thorpe, the Office contends, teaches a cleavable peptide linker inside a fusion protein. *Id.* at 3 and 4. Combining these references, the Office concludes that it would have been obvious to one of ordinary skill in the art to modify the methods taught by the references to make a bifunctional, chimeric molecule comprising D-amino acids that enters the cell and induces apoptosis. *Id.* at 4. The Office contends that one would have been motivated to do so because killing cells via apoptosis minimizes tissue damage or systemic response, as allegedly taught in Aqeilan. *Id.* According to the Office, the skilled artisan would have a reasonable expectation of success in light of the alleged teaching in Aqeilan and because SEQ ID NO: 239 and 269 are described in the art. *Id.* Applicants respectfully traverse.

Solely to facilitate prosecution and without acquiescing in the rejection, Applicants have amended claims 46, 70, 72, 74, 76, 78, and 80 to include a mitochondrial localization sequence ("MLS"). Neither Aqeilan, Kim, Huang, Bredesen, Sela, nor Thorpe teach the use of a MLS in a Targ/Tox chimeric, bifunctional molecule. Because none of these references teach this element of independent claims 46, 70, 72, 74, 76, 78, and 80, the combination of these references could not have rendered claims 46 and 69-84 obvious. Applicants therefore request that the Office withdraw this rejection.

Conclusions

Applicants respectfully request that the Office enter this Amendment under 37 C.F.R. § 1.116, placing claims 46 and 69-84 in condition for allowance.

Furthermore, Applicants submit that the entry of the amendment would place the application in better form for appeal, should the Office dispute the patentability of the pending claims.

In view of the foregoing remarks, the claimed invention is not rendered obvious in view of the prior art references cited against this application. Applicants therefore request the entry of this Amendment, the Office's reconsideration and reexamination of the application, and the timely allowance of claims 46 and 69-84.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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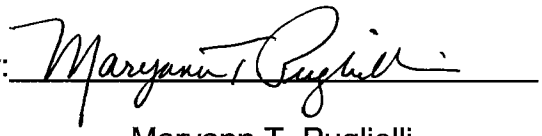
By: 

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